Claim 6 was objected to as not complying with 37 C.F.R. § 1.821(a)(2)(D). Applicants have amended the claim the remove the nucleotide sequences and replace them with sequence identifiers.

Claim 16 was objected to as being dependent on a claim to a non-elected embodiment. The claim has been amended to correctly depend on claim 15 and thus no longer depends on a non-elected invention.

Claims 17 and 29 were rejected under 35 U.S.C. § 112, first paragraph as not enabled. In their most previous amendment, Applicants argued to overcome this rejection as follows:

> A medicament is based upon the inactivation or removal of the met DNA. Since the sequence of the met DNA is known, methods based upon the DNA sequence will have the required specificity to target the met DNA. *Scanlon et al.*, (1995): Oligonucleotide-Mediated Modulation of Mammalian Gene Expression. Faseb J. 9, 1288-1296. Inactivation of the met DNA was envisaged to be achieved by using specific DNA designed to form an inactivating triple helix structures with the met DNA. *Tu et. al.* (1995), Inhibition of Gene Expression By Triple Helix Formation In Hepatoma Cells; J of Biol. Chem. 270: 28402-28407, *Wang et. al.*, (1995), Targeted Mutagenesis in Mammalian Cells Mediated By Intracellular Triple helix Formation- a New Approach to Gene Therapy; J. of Cell. Biochem., 385-386. The specific degradation of the met DNA can be achieved by complexing to the triple helix forming DNA an inactivating or DNA degrading chemical or reagent. *Kane et al.* Specific Cleavage of a Triple Helix by Fe-II Center Dot Bleomycin, Biochem. 34: 16715-16724; *Shields et. al.*; Sequence Selective DNA Recognition and Photocleavage- A Comparison of Enantiomors of Rh(En)(2)Phi(3+); Biochem. 34, 15037-15048. These techniques had been widely published before the priority date of the patent as evidenced by the publication dates of the references. Applicant's submit that the claims are in compliance with 35 U.S.C. § 112, first paragraph.

Applicants respectfully apologize for not including the cited references in its previous amendment. These references are attached. Applicants respectfully request reconsideration of their argument in light of these references.

The Examiner additionally argues that the specification does not provide guidance as to what disease would be treated, what doses are administered and the result of any treatment. Applicants respectfully argue that, as the Examiner noted, the specification does indicate that the oligonucleotides could be used for the treatment of cancer. Applicants additionally argue that since the claim is to a medicament, and not a method, that the doses and result of the treatment are not relevant to the claim. Applicants respectfully argue that claims of this type are commonly issued based on similar disclosures that do not include dosage or result of the treatment as discussed above (see, *e.g.*, U.S. Patent No. 5,272,065, claim 146).

Claims 1-5, 18 and 19 were rejected under 35 U.S.C. § 112, first paragraph, as non-enabled. Applicants traverse this objection. There is nothing in the art to suggest that benign tumor producing cell lines other than Rama 37 should be treated differently. The Examiner appears to argue that there is nothing in the present application to indicate that any DNA fragment from any malignant cell when introduced into a benign cell will induce "transformation." The whole essence of the application is that the fragments have to be of the specific sequence as indicated. The Applicants have indicated an efficacious size of fragment. The method of producing benign, non-metastasizing tumors in animals is well known — an artisan of skill could easily have read the derivation of the cell lines used. The skilled artisan would have induced tumors in an animal using standard carcinogens ("DMBA, NMU") and would have isolated cell lines therefrom as was done and published in deriving Rama 37 cells. They would then have derived DNA fragments as described in the application and selected the appropriate ones using the recipient animals as the selection method, as described in this application. The individual methods (except for the use of tags to identify the fragments) are and were standard in the field. Their use has been described in, for example, Davies BR et al. Cancer Research 54: 2785-2793, 1994 (previously cited by Examiner).

Claims 1-7, 11, 15, 17-19, 23 and 29 were rejected under 35 U.S.C. § 112, second paragraph as being indefinite.

Claim 1 was rejected as vague because the Examiner thought it was unclear as to what was being qualified by the phrase "which have been tagged . . .". Although Applicants contend that the language was clear, the claim has been amended. Applicants respectfully request removal of this rejection.

Claim 6 was rejected as lacking antecedent basis for the term "the double-stranded synthetic oligonucleotide's tag." Although Applicants contend that there was proper antecedent basis, this claim has been amended to make this language more clear.

Claim 7 was rejected as vague because the Examiner felt it was unclear as to what was qualified by the term "consisting essentially of." Although Applicants believe the language was clear, the claim has been amended.

Applicants submit that the claims are now compliant with 35 U.S.C. § 112. Withdrawal of these rejections is respectfully solicited.

Claims 15, 18, and 19 were rejected under 35 U.S.C. § 102(a) as being anticipated by Chen et al. Applicants respectfully contend that the Examiner has not established a *prima facie* case that Chen is prior art. The priority date of this application is January 10, 1996. To qualify as prior art, the Examiner must conclusively establish that Chen was published within the first ten days of 1996 (if, as cited by the Examiner, the article was published in 1996). Applicants' understanding is that Chen et al. was presented at a poster session at an April 16-18, 1996 meeting and was subsequently published in Biochemical Society Transactions. Thus, Chen et al. is not prior art. Withdrawal of this rejection is respectfully requested.

Claims 15 and 23 were rejected under 35 U.S.C. § 102(e) as being anticipated by Sazaki et al. Sazaki et al. teach a DNA sequence of almost 7,000 bases of which only 17 bases align with 17 bases from the nearly 1100 bases disclosed in the present application. Applicants submit that Sazaki et al. hardly provide the means to design a specific probe given its large size, particularly as the use is totally different from that envisioned in the present

application, namely identifying a bug involved in otitis media. Applicants respectfully request removal of this rejection.

Applicants have made a genuine effort to respond to the Examiner's rejections in advancing the prosecution of this case. Applicants believe all formal and substantive requirements for patentability have been met and that this case is in condition for allowance, which action is respectfully requested.

The Examiner is requested to telephone the undersigned to discuss resolution of any issues necessary to place this case in condition for allowance. Please charge any additional fees or credit any overpayment s as the result of the filing of this paper to our Deposit Account No. 02-3978.

Respectfully submitted,

PHILIP S. RUDLAND ET AL.

By _____
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Date: ***October 8, 2002***

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Attachment

VERSION WITH MARKINGS TO SHOW CHANGES MADE

In The Claims

1. (Twice Amended) A method of screening and recovering a regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis comprising the steps of:

i. transferring fragments of human DNA of less than 1.5 kb in length, said fragments having [from malignant, metastatic cancer cells which have] been tagged at both ends with double-stranded synthetic oligonucleotides that provide restriction enzyme and unique primer [cites] sites, from malignant, metastatic cancer cells, into a cell line that produces only benign, non-metastasizing tumours when injected into a syngeneic animal;

ii. injecting the transformed cells into the syngeneic animal;

iii. selecting those animals in which metastasizing tumours have been identified; and

iv. recovering the regulatory DNA capable of inducing metastasis therefrom.

6. (Twice Amended) The method of claim 5 wherein the fragments are tagged with a double-stranded synthetic oligonucleotide, one strand whose sequence is SEQ. ID. No. 7 and the other strand whose sequence is SEQ. ID. NO. 8. [tag has the following oligonucleotide sequence:

Primer

5'AATCCAAGCTTGCGGCCGATCAGGCCGAATATGCGGCCGCATTAT-3'
AGGTTCGAACGCCGGCTAGTCCGGCTTATACGCCGGCGTAATATCGA

*Hind*III *Sfi*I *Not*I Defective *Hind*III]

7. (Twice Amended) A regulatory DNA which is not expressed as an mRNA but is capable of inducing metastasis, said regulatory DNA consisting essentially of a human DNA fragment of less than 1.5 kb in length and comprising [a] the sequence [selected from the group consisting] of [SEQ. ID. NO. 1, SEQ. ID. NO. 2, SEQ. ID. NO. 3,] SEQ. ID. NO. 4, [SEQ. ID. NO. 5, and SEQ. ID. NO. 6,] obtained from a malignant, metastasis cancer cell.

16. (Twice Amended) A kit for diagnosing the likelihood of a cancer metastasizing comprising a probe of claim [13] 15 and one or more of a color indicator, an oligonucleotide primer, materials for gel analysis and materials for DNA transfer or hydridisation.